REMARKS

The Claim Amendments

In order to advance prosecution, Applicants have amended claim 1 and dependent claims 3, 14-23, 32 and 35 and have canceled claims 2, 10-13, and 24. Claims 4-9, 25-31, and 33-34 were previously canceled. Specifically, claim 1 has been amended to recite a chemically modified double-stranded short interfering ribonucleic acid (siRNA) molecule comprising a complementary sense strand and antisense strand, wherein: said sense strand and said antisense strand are each independently about 14 to 28 nucleotides in length; said antisense strand comprises about 14 to 28 nucleotides that are complementary to a vascular endothelial growth factor receptor 1 (VEGFr1) nucleotide sequence corresponding to SEQ ID NO:2752 or a portion thereof and vascular endothelial growth factor receptor 2 (VEGFr2) nucleotide sequence corresponding to SEQ ID NO:2753 or a portion thereof; said sense strand of said siRNA molecule comprises a portion of said VEGFr1 and VEGFr2 nucleotide sequence of about 18 to about 27 nucleotides; and said siRNA molecule comprises at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide.

Support for the amendments to claim 1 can be found, inter alia, at pages 7-12 (chemically modified siRNA, sense strand and antisense strand, antisense strand complementarity to VEGFR1 and VEGFR2 sequence); pages 17, 21, and 30-31 (2'-O-methyl and 2'-deoxy-2'-fluoro modifications); page 21 (about 14 to about 28 nucleotides in length; see also page 9 of USSN 60/334461 which is incorporated by reference); and pages 7, 8, 9, 12, 57, 76, and 160-221 (referring to GenBank Accession No. NM_002019 for VEGFR1 RNA, SEQ ID NO:2752 and GenBank Accession No. NM_002253 for VEGFR2 RNA, SEQ ID NO:2753). Claim 1 and dependent claims 3, 14-21, 30 and 33 have been amended to recite the term "siRNA" rather than "siNA". Support for these amendments can be found, inter alia, at pages 1, 7, 12, 71 and throughout the

specification. Claims 14-16, 18-21, and 30 have been amended to recite the term "strand" instead of "region". Support for these amendments can be found, inter alia, at pages 12, 13, 18, 24-27, 29-36 and throughout the application. Claims 14, 15, and 18-20 have been amended to recite the term "one or more". Support for these amendments can be found, inter alia, at pages 20-22, 25, 28, and 30-31. Claim 30 has been amended to recite the term "terminal" with regard to the claimed phosphate group. Support for this amendment can be found, inter alia, at page 32. Claim 69 has been amended to recite the term "pharmaceutically acceptable carrier or diluent". Support for the amendment can be found, inter alia, at pages 59 and 110.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

The Sequence Listing

Applicants have enclosed a new sequence listing and request its entry in place of the previously entered sequence listing. The sequence listing adds SEQ ID NOS:2752 and 2753. The sequence represents GenBank entry NM_002019 (as of October 31, 2000) for SEQ ID NO:2752 and GenBank entry NM_002253 (as of March 14, 2001) for SEQ ID NO:2753 (see Tables I and II). Applicant submits that the CD-R submitted in lieu of the paper copy and the CD-R submitted for the computer-readable copy are identical in content. The sequence listing adds no new matter and applicants respectfully request its entry.

Priority

The Office Action alleges that the instant application is not entitled to the priority date earlier than February 20, 2003, which is the filing date of PCT/US03/05022, because support for the range "about 19 to about 29" is not found in any of the earlier priority documents (see Office Action at page 3). The Applicant respectfully disagrees with the Office's assessment of the priority claim because even the earliest priority document, USSN 60/334461, filed November 30, 2001 (the '461 application), contains the following language at page 9, lines 10-13:

> In one embodiment, a single strand component of a siRNA molecule of the invention is from about 14 to about 50 nucleotides in length. In another embodiment, a single strand component of a siRNA molecule of the invention is about 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 nucleotides in length.

The range of 19 to 29 nucleotides is clearly within the range of 14 to 50 nucleotides as described in the '461 application. However, in the interest of expediting prosecution, claim 1 has been amended to recite a range of about 14 to 28 nucleotides, which is expressly supported by the range described on page 9, lines 12-13 of the '461 application. It should be noted that the '461 application also discloses GenBank entry NM_002019, which corresponds to SEQ ID NO:2752 and GenBank entry NM_002253, which corresponds to SEQ ID NO:2753, on page 6, lines 20-21. Thus, the instant application properly claims priority to, *inter alia*, the '461 application. Applicant respectfully submits that the instantly claimed invention is entitled to a priority date of at least November 30, 2001.

Claim Objections

Claim 1 was objected to because it allegedly ended in an ",.". The version of Claim 1 appearing on PAIR does not appear to have a ",." because the comma after the word "thereof" has been stricken from the claim as follows: "thereof~~, and wherein said...~~". Nevertheless, in the interest of expediting prosecution, Claim 1 has been

amended to remove a comma next to the period at the end of the claim, thus obviating the objection.

Claim 35 was objected to because it allegedly recited "in pharmaceutically acceptable carrier" rather than "in a pharmaceutically acceptable carrier". The version of Claim 35 appearing on PAIR shows that the work "an" was amended to "a" as follows: "a~~n~~". Nevertheless, in the interest of expediting prosecution, Claim 35 has been amended to recite the term "in a pharmaceutically acceptable carrier", thus obviating the objection.

Obviousness-Type Double Patenting Rejection

Claims 1-3, 10-24, 32 and 35 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being obvious over claims 1-30 of copending Application No. 10/664,668 and claims 49-51 and 58-76 of copending Application No. 10/444,853.

Without acceding to the merits of the rejection, Applicant will consider filing a terminal disclaimer upon allowance of the pending claims.

35 U.S.C. § 112 Rejection

Claims 1-3, 10-24, 32 and 35 were rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 2, 10-13, and 24 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 14-23, 32 and 35.

The Office Action asserts that the specification "fails to provide an adequate written description of the broad genus of compounds as claimed because the specification does not provide a representative number of species of the claimed compounds." (see Office Action, page 10). The Office Action concludes that "Applicant has not shown

how the invention was 'ready for patenting' such as by the disclosure of a representative number of species from within the broad genus of compounds now claimed or by describing distinguishing identifying characteristics of the claimed compounds that is sufficient to show that the applicant was in possession of the instant invention, commensurate with the breadth of what is claimed." (see Office Action, page 11).

Applicants respectfully disagree with this argument because the specification teaches how to design, synthesize, and test siNA molecules targeting any VEGFR1 and VEGFR2 target sequence having sequence homology and provides numerous examples of other VEGFR1 and VEGFR2 RNA target sequences via GenBank Accession numbers listed in Table I of the instant specification. Furthermore, the specification provides numerous examples of actual siRNA constructs that target both VEGFR1 and VEGFR2 RNA (via homologous sequence analysis, see for example Table II), including chemically modified variants of such siRNA molecules as are presently claimed (see for example Table III), and demonstrates inhibition of VEGFR1 and VEGFR2 gene expression using such siRNA molecules (see, for example, Figures 22 and 23 and the corresponding descriptions thereof on pages 93 and 143). Applicant has therefore clearly demonstrated that the invention was 'ready for patenting' by disclosing a representative number of species and by describing distinguishing identifying characteristics of the claimed compounds that is sufficient to show that the applicant was in possession of the instant invention, commensurate with the breadth of what is claimed as demonstrated by an actual reduction to practice of the claimed invention.

Despite these teachings, in the interest of expediting prosecution, claim 1 has been amended and is now directed to a chemically modified double-stranded short interfering ribonucleic acid (siRNA) molecule comprising a complementary sense strand and antisense strand, wherein: said sense strand and said antisense strand are each independently about 14 to 28 nucleotides in length; said antisense strand comprises about 14 to 28 nucleotides that are complementary to a vascular endothelial growth factor receptor 1 (VEGFr1) nucleotide sequence corresponding to SEQ ID NO:2752 or a portion thereof and vascular endothelial growth factor receptor 2 (VEGFr2) nucleotide

sequence corresponding to SEQ ID NO:2753 or a portion thereof; said sense strand of said siRNA molecule comprises a portion of said VEGFr1 and VEGFr2 nucleotide sequence of about 18 to about 27 nucleotides; and said siRNA molecule comprises at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide. Examples of actual siRNA constructs that target both VEGFR1 corresponding to SEQ ID NO: 2752 and VEGFR2 RNA corresponding to SEQ ID NO: 2753 are shown in Tables II and III). Furthermore, examples of siRNA molecules that inhibit VEGFR1 (SEQ ID NO: 2752) and VEGFR2 (SEQ ID NO: 2753) RNA gene expression are provided (see, for example, Figures 22 and 23 and the corresponding descriptions thereof on pages 93 and 143). Thus, contrary to the Office's assertion, the specification provides a representative number of species of the claimed compounds and thus provides an adequate written description of the claimed compounds.

The claim as amended is fully supported by the written description of the application and priority documents as discussed in detail above under the discussion of priority. Accordingly, applicant respectfully requests withdrawal of the 35 U.S.C. §112, first paragraph, rejection.

35 U.S.C. § 102 Rejections

Claims 1-3, 11-24, 32 and 35 were rejected under 35 U.S.C. 102(e) as being anticipated by Lockridge *et al.* (US 2003/0216335). Claims 2, 11-13, 23, and 24 have been canceled, thus rendering the rejection moot as applied to these claims. Applicants respectfully traverse the rejection with respect to claims 1, 3, 14-23, 32 and 35.

Lockridge *et al.* (US 2003/0216335) is claimed in the instant application under the priority paragraph as originally filed (see page 1, line 15) and is incorporated by reference in its entirety. The office action alleges that "although Lockridge *et al.* is claimed in the instant application for the benefit of a prior-filed application, the disclosure of Lockridge *et al.* is not considered to provide [sic] support a claim to the benefit of priority of an earlier filed document as above." (see Office Action, page 12). Furthermore, the Office Action alleges that "although the disclosure of Lockridge *et al.*

(as supported by Provisional Application 60/334,461) does not provide support for the claimed length range of about 19 to about 29 as instantly claimed, the disclosure of Lockridge sets forth particular double stranded nucleic acid molecules, the length of which fall within the instantly claimed size range and are therefore reasonably considered to anticipate the instant invention." (see Office Action, page 12). Applicants respectfully traverse this argument for the following reasons.

Claim 1 has been amended to recite a range of about 14 to 28 nucleotides, which is expressly supported by the range described on page 9, lines 12-13 of the 60/334461 application, to which the instant application claims priority. The priority date of the instant application is therefore the filing date of the 60/334461 application, which is November 30, 2001. The 102(e) date of the Lockridge US 2003/0216335 application is November 30, 2001. Given that the priority date of the instant application and the Lockridge reference are the same date, Lockridge is not considered proper prior art.

Furthermore, as acknowledged in the Office Action on page 12, the instant application claims priority to the Lockridge US 2003/0216335 application. However, contrary to the Office's allegation that Lockridge does not provide sufficient support for a claim of priority, the Lockridge reference expressly teaches an siRNA molecule of the claimed length range, i.e., 14-28 nucleotides, on page 4, paragraph [0040]. Thus, the presently claimed invention is fully supported by the disclosure in Lockridge, making the instant claim of priority to Lockridge proper. For the reasons set forth above, Applicant submits that Lockridge is not a prior art reference and does not anticipate the instant application. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 102(e) rejection based on Lockridge *et al.*

Claims 1, 3 and 35 were rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir *et al.* 2001 (Nature, Vol. 411). Applicants respectfully traverse the rejection.

The Office Action alleges that because the language of the presently claimed invention is non-limiting, and because Elbashir discloses a siRNA construct (uGL2) which comprises a "CCU" in the antisense strand and because "CCU" is complementary

to a portion of SEQ ID NO:2275 (a homologous VEGFR1/VEGFR2 target sequence) of the instant application, Elbashir anticipates claims 1, 3, and 35. Without acceding to the merits of this argument, Applicant has amended Claim 1 to read "said antisense strand comprises about 14 to 28 nucleotides that are complementary to a vascular endothelial growth factor receptor 1 (VEGFr1) nucleotide sequence corresponding to SEQ ID NO:2752 or a portion thereof and vascular endothelial growth factor receptor 2 (VEGFr2) nucleotide sequence corresponding to SEQ ID NO:2753 or a portion thereof". There is no siRNA sequence disclosed in Elbashir that comprises about 14 to 28 nucleotides that are complementary to VEGFr1 sequence corresponding to SEQ ID NO:2752 or a portion thereof and VEGFr2 sequence corresponding to SEQ ID NO:2753 or a portion thereof as presently claimed. Accordingly, Elbashir et al. does not anticipate because it does not teach the presently claimed invention and Applicant respectfully requests withdrawal of the 35 U.S.C. § 102(b) rejection based on Elbashir *et al.*

Claims 1-3, 11-24, 32 and 35 were rejected under 35 U.S.C. 102(e) as being anticipated by Pavco *et al.* (US 6,346,398). Claims 2, 11-13, 23, and 24 have been canceled, thus rendering the rejection moot as applied to these claims. Applicants respectfully traverse the rejection with respect to claims 1, 3, 14-23, 32 and 35.

Pavco *et al.* disclose various ribozyme nucleic acid molecules. Pavco et al. do not teach siRNA molecules. The Office Action alleges that Pavco *et al.* "disclose the use of a nucleic acid based compound to inhibit the expression of VEGFR1 and VEGFR2" and that "nucleic acids of the invention are chemically synthesized double stranded nucleic acids (siRNAs) that comprise single stranded sense and antisense strands of 23 nucleotides" (see Office Action pages 14-15). Applicants respectfully traverse these alleged features of Pavco *et al.* in relation to the presently claimed invention. Claims 1, 3, 14-23, 32 and 35 have been amended to recite the term "siRNA" rather than "double stranded nucleic acid molecule". Furthermore, claim 1 has been amended to recite "A chemically modified double-stranded short interfering ribonucleic acid (siRNA) molecule comprising a complementary sense strand and antisense strand". The terms "siRNA", "sense strand", or "antisense strand" are not found anywhere in Pavco *et al.* The term

"siRNA" as used in the instantly claimed invention is defined as a nucleic acid molecule capable of inhibiting or down regulating gene expression or viral replication, by mediating RNA interference or "RNAi". None of the nucleic acid molecules described in Pavco *et al.* would be expected to mediate RNA interference because ribozymes and antisense molecules are fundamentally different from siRNA molecules.

Aside from this functional distinction, the siRNA molecules as presently claimed can be distinguished structurally as well. Whereas ribozymes and antisense molecules have regions that are complementary to target nucleic acids for down regulation of gene expression (the Office Action appears to consider such regions to be an "antisense strand"), they do not have have a sense strand that has sequence of the target nucleic acid (i.e. sequence corresponding to the target sequence), as do the presently claimed siRNA molecules. To emphasize this structural distinction and to expedite prosecution, claim 1 has been amended to include the language "said sense strand of said siRNA molecule comprises a portion of said VEGFr1 and VEGFr2 nucleotide sequence of about 18 to about 27 nucleotides" to better distinguish the claimed siRNA molecules. This feature is not found in Pavco *et al.*

Accordingly, Pavco et al. does not anticipate because it does not teach each and all of the limitations of the presently claimed invention. Therefore, Applicant respectfully requests withdrawal of the 35 U.S.C. § 102(e) rejection based on Pavco *et al.*

35 U.S.C. § 103 Rejections

Claims 1-3, 11-24, 32 and 35 were rejected under 35 U.S.C. 103(a) as being unpatentable over Pavco *et al.* (US 6,346,398), Sirois *et al.* (US 2003/0186920 A1), Fire *et al.* (WO 99/32619), Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888), and Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087). Claims 2, 11-13, 23, and 24 have been canceled, thus rendering the rejection moot as applied to these claims. Applicants respectfully traverse the rejection with respect to claims 1, 3, 14-23, 32 and 35.

Applicants submit that Sirois *et al.* is not prior art to the instantly claimed invention because Sirois *et al.* was published after the effective filing date of the instantly claimed invention (see discussion of Priority above). This alone is sufficient to obviate the present 35 U.S.C. 103(a) rejection. Furthermore, as described above, Pavco has been clearly distinguished by the present claim amendments.

However, even considering the teachings of Sirois *et al.,* and Pavco *et al.,* Applicants submit that the Office Action has still not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

In the present case, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings to arrive at the presently claimed invention. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

An examiner can satisfy the burden required for obviousness in light of combination "only by showing some objective teaching [leading to the combination]." *See, In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes

the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317(Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed").

Applicant submits that one of skill in the art would not have been motivated to combine the cited references to arrive at the presently claimed invention. Elbashir is the only reference cited that teaches a general structure of the claimed nucleic acid molecules, *i.e.*, a short double stranded RNA molecule having one strand complementary to a target RNA and another strand having sequence comprising a portion of the target RNA sequence. All of the other references describe either long double stranded RNA (Fire and Parrish), antisense (Sirois *et al.*) or ribozyme art (Pavco *et al.*). Although long double stranded RNA, antisense, and ribozymes are nucleic acid based technologies, they differ substantially from the present invention both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active. Just as ribozyme and antisense modifications are not amenable to long double stranded RNA and vice versa, neither of these nucleic acid technologies provides any insight or guidance into chemical modification of the siRNAs as described by Elbashir.

Elbashir *et al*, was the first publication that studied the effect of chemical modifications on short interfering RNA (siRNA), i.e. the capacity of modified siRNA to mediate RNA interference. The results published by Elbashir clearly teach away from the presently claimed invention. Elbashir attempted to apply chemical modifications to

siRNA based on the teachings of the prior art, including Parrish (see for example Elbashir *et al.*, 2001, Genes and Development, 15:188-200, and which references the work of Parrish at page 198), but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. These molecules were found to have significantly diminished activity or were totally inactive in inducing target specific cleavage by RNAi. For example, the discussion on pages 6881 and 6882 of Elbashir describes siRNA duplexes having internal base paired modifications (2'-deoxy and 2'-O-methyl) and is reproduced below:

> To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of the siRNA duplex were replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-O-methyl residues.

Figure 4 of Elbashir clearly shows that only limited 2'-deoxy substitutions at the 3'-end of a siRNA molecule could be tolerated. Importantly, in all cases where substantial internal base paired substitutions were used, such modification was shown not to be tolerated for RNAi. In addition, according to "*The siRNA Users Guide*" on page 6885 of Elbahsir,

> 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

It is important to understand that because the first sentence quoted above references only 2'-deoxy modifications and not 2'-O-methyl modifications, the term "More extensive" in the second sentence can modify only "2'-deoxy" in the second sentence and not "2-O-methyl." The beginning of the second sentence is equivalent to "2'-O-methyl and more extensive 2'-deoxy modifications reduce the ability of siRNAs to mediate RNAi." Thus, Elbashir flatly states that 2'-O-methyl modifications should be avoided.

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The Office action states that "One of ordinary skill in the art would have been motivated and expected success in chemically synthesizing an siRNA as above (referring to various chemical modifications) in order to use a nuclease resistant inhibitory nucleic acid with enhanced cellular uptake to study the particular function of the VEGFR1 and VEGFR2 genes...because the structural features of effective siRNA duplexes were known as taught by Elbashir..." (see Office Action at page 20). However, based on the teachings of "[t]he siRNA Users Guide" from Elbashir, one of skill in the art would have avoided making any modifications beyond the 2'-deoxynucleotide substitutions at the 3'-end of the siRNA molecule and certainly would not have been motivated to pursue the presently claimed invention, *i.e.*, a chemically modified siRNA molecule having at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide. How could one have been motivated to make more extensive modifications when the **only** piece of prior art dealing directly with short double stranded RNA molecules expressly states that more extensive modifications result in decreased activity?

This conclusion is further supported by publications in the field in the 2001 and 2002 time frame, where experts in the field followed the teachings of Elbashir *et al.*, 2001, EMBO J. Vol. 20, No. 23, pages 6877-6888 and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA (*see, e.g.,* Bitko *et al.,* 2001, BMC Microbiology, 1, 34 page 9, left column under heading Materials and Methods section; Kumar *et al.*, 2002, Malaria Journal, 1:5, page 9, right column, under heading Transfection by Inhibitory dsRNA"; and Holen *et al.,* 2002, Nucleic Acids Research, 30, 1757-1766, Figures 1, 2 and 6). These prior art references demonstrate that Elbashir taught away from the presently claimed invention and not just from 100% modified duplexes. If it would have been obvious, clearly, the presently claimed invention would have been practiced by those of skill in the art, including Elbashir and those that followed Elbashir's teaching.

The above argument is best explained by a plain reading of Elbashir, which teaches that no modifications other than 3'-terminal deoxy nucleotides are not tolerated and likely interfere with protein association in siRNP assembly. As such, Elbashir did

not provide any motivation to a person skilled in the art to take the teachings of the prior art, e.g., long dsRNA, antisense or ribozymes, and apply it to short double stranded RNA molecules as presently claimed because Elbashir tried this approach and failed; Elbashir therefore teaches away from using modifications beyond use of 2'-deoxynucleotides at the 3'-terminal positions of the short double stranded RNA molecules and not just 100% modification. One of skill in the art would not have been motivated to incorporate 2'-O-methyl or 2'-deoxy-2'-fluoro modifications within a siRNA molecule as is presently claimed.

With regard to Parrish, the Office Action states that "Parrish *et al.* teach RNA interference using double stranded nucleic acids that are comprised of alpha thio nucleotide analogues (see Figure 5), reasonably considered here to read on double stranded nucleic acids that comprise no ribonucleotides". (see Office action, page 18) First, substitution with phosphorothioates (alpha thio nucleosides), which is a nucleic acid backbone modification, has no bearing on ribonucleotide modifications, as ribonucleotide modifications impact the 2'-OH position of the ribose sugar. In addition, substitution with phosphorothioates at more than two residue positions in the work of Parrish *et al.* resulted in inactive double stranded RNAs: "modification of more than two residues greatly destabilized the RNAs in vitro and we were not able to assay interference activities" (see Parrish *et al.*, page 1081). Therefore, Parrish *et al.* does not teach double stranded nucleic acids that comprise no ribonucleotides.

The Office Action appears to cite Parrish with reference to claim 2, which has been canceled. However, for the record, Applicant wishes to address the relevance of Parrish to the presently claimed invention in general, and sets forth the proposition that Parrish does not provide any guidance or teaching of how to chemically modify short interfering RNA as are presently claimed. Claims 1, 3, 14-23, 32 and 35 have been amended to recite the term "siRNA" rather than "double stranded nucleic acid molecule", and claim 1 has also been amended to recite "said siRNA molecule comprises at least one 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide". The Parrish *et al.* reference does not teach modified siRNA, as all of the modified constructs tested by Parrish *et al.* were long

double stranded RNAs (as described below) that were prepared using enzymatic methods. The paper by Parrish represents a broad survey of the biochemical properties of the RNAi reaction in nematodes using long dsRNAs, but it does not provide any useful information regarding the design of modified siRNA molecules, including chemically modified siRNA. In 2000–2001 it was clear that RNAi was a conserved cellular mechanism that was present in a diverse set of organisms; it was first discovered in plants, then in nematodes, ciliates, fungi, Drosophila, and finally in mammalian cells (see for example Elbashir *et al*). But while the basic mechanism is conserved, it was clear to those skilled in the art that the mechanistic details could be very different from one organism to another, as is evidenced by publications at the time. Specifically, the lower Eukaryotes are easily activated by long dsRNA, while publications such as Elbashir *et al.*, 2001, EMBO J., Vol 20, No. 23, pages 6877-6888, noted that long dsRNA failed to stimulate RNAi in mammalian cells; this was likely due to the activation of an interferon response in mammalian cells, which is absent in the lower Eukaryotes. Likewise, Bernstein *et al* (2001, *RNA* **7**:1509-1521) noted that *C. elegans* and plants have a number of RNAi-related behaviors that are not found in mammalian cells, including the ability to pass the RNAi effect from one cell to the next, the ability to amplify the RNAi response such that a few dsRNA molecules can elicit a potent RNAi response, and the ability to pass the RNAi response from one cell generation to the next due to the long-lived nature of RNAi in these organisms (p1515-1516). These profound differences would teach those skilled in the art that it is unwise to generalize discoveries made in *C. elegans* to the world of mammalian RNAi.

A second factor that makes it difficult to draw lessons from Parrish *et al.* is that all of the studies were performed using long dsRNA. The shortest dsRNA molecules used were 26 & 27 bp, but these were only used for initial base composition studies and not for chemical modification studies. In fact, Parrish clearly states that any molecules less than 26 bps were inactive (p1079, right column). The nucleotide modification studies were performed primarily using a 742 bp *unc*-22A sequence that apparently also contained "3–30 nt of dsRNA derived from polylinker sequences on each end, and polylinker-derived single stranded tails of 10–30 nt." (Materials & Methods, p1085). The authors checked

the annealing of these sequences by agarose gel, but that would only confirm that they were stuck together, not whether they were annealed properly. These long sequences add a great deal of ambiguity to the interpretation of the results. An "inactive" modification could be such because it failed to allow the strands to anneal properly rather than being deleterious to the RNAi machinery, and an "active" modification could actually be an inactive modification that is distributed sparsely enough on the sequence that the RNAi machinery can still function. This latter possibility is of particular concern since Parrish reports that they "were able to demonstrate interference activity following incorporation of any single modified residue", but that "RNAs with two modified bases also had substantial decreases in effectiveness as RNAi triggers." (p1081, right column). Thus, the modifications have a cumulative effect such as would be expected if the RNAi machinery was finding unmodified places on the long dsRNA to bind and activate.

One final argument against Parrish is that they themselves were unable to formulate a cogent conclusion to their chemical modification studies. They tested over 30 combinations of chemical modifications (their Figure 5, Figure 6, and data not shown), but in the discussion section they can only muster three short paragraphs speculating on the possible implications of these studies (p1084, left column). Their conclusions are: (1) the dsRNA might need to maintain an A-form helix to be active, (2) the antisense strand is more sensitive to modification than the sense strand, and (3) some modifications affect RNAi activity when added to either strand. These speculations are only weakly supported by the data. Coupled with the concerns mentioned above regarding long dsRNA and the difficulty of extending observations from *C. elegans* to mammalian cells, these considerations would have made it very difficult for one of skill in the art to draw any conclusions whatsoever from Parrish regarding the design of short siRNA molecules.

For all of the reasons set forth above, one skilled in the art would not have had a reasonable expectation that the chemical modifications applied to ribozyme, antisense, and long dsRNA could have been successfully applied to siRNA molecules. Moreover, as discussed above, Elbashir and Parrish, as well as other references representing the state

of the art, actually teach away from incorporating 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotide modifications into siRNA molecules.

Thus, the cited references, alone or in combination, do not provide a reasonable expectation of success, as is clearly shown from the teachings of Elbashir and the state of the art following Elbashir. The existence or lack of a reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art at the time the invention was made. *See, Micro Chem. Inc. v. Great Plains Chem. Co.,* 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236, 1245 (Fed. Cir. 1997). The inventors' ultimate success is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See, Standard Oil Co. v. American Cyanamid Co*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, one can not use the inventors' success as evidence that the success would have been expected. *See, In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316, (Fed. Cir. 2000).

Applicant submits that no *prima facie* case of obviousness exists because there would have been no motivation to combine the cited references, no reasonable expectation of success in such a combination, and finally, the cited references in combination do not properly teach the presently claimed invention, and in fact, teach away from the instant claims. Because no prima facie case of obviousness has been established, the applicant's respectfully submit that the Office has used improper hindsight reasoning in rejecting the claims.

The applicants are the first ones to show that selective incorporation of 2'-O-methyl and 2'-deoxy-2'-fluoro modifications are well tolerated in siRNA molecules targeting gene expression, as evidenced by the fact that the applicants were the first to utilize double stranded nucleic acid molecules as presently claimed to successfully down regulate gene expression. For example, in the instant application USSN 10/758,155, published as US-2005-0075304-A1, Applicant has designed, synthesized, and tested the presently claimed 2'-deoxy-2'-fluoro and 2'-O-methyl modified siRNA molecules having potent activity directed against VEGFR1 and VEGFR2 gene expression (see for example Figures 22 and 23 and their corresponding descriptions on pages 93 and 143).

In addition, in co-pending application USSN 10/444,853, published as US-2004-0192626, applicant has designed, synthesized, and tested several 2'-deoxy-2'-fluoro and 2'-O-methyl modified siRNA molecules having potent activity directed against several different gene targets (see for example Figure 6 with a corresponding description on page 28, paragraph [0219], Figure 7, with a corresponding description on page 28, paragraph [0220], both described in Example 5 starting on page 68 and with sequences shown in Table I; see also Figures 11-15). These co-pending applications demonstrate that application of 2'-deoxy-2'-fluoro and 2'-O-methyl modifications to siRNA structures are well tolerated for maintaining potent RNAi activity against VEGFR1/VEGFR2 and other target nucleic acid sequences.

For the reasons set forth above, Sirois *et al.* is not prior art to the present invention. Furthermore, a person skilled in the art would not have been motivated to follow the teachings of Elbashir, let alone Parrish or the antisense and ribozyme art, to make and use the double stranded nucleic acid molecules of the present invention to target human VEGFR1 and VEGFR2 gene expression. Thus, Pavco *et al.* (US 6,346,398), Sirois *et al.* (US 2003/0186920 A1), Fire *et al.* (WO 99/32619), Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888), and Parrish *et al.* (Molecular Cell, 2000, Vol. 6, pages 1077-1087), alone or in combination, do not render the present claims obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections based on these teachings.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

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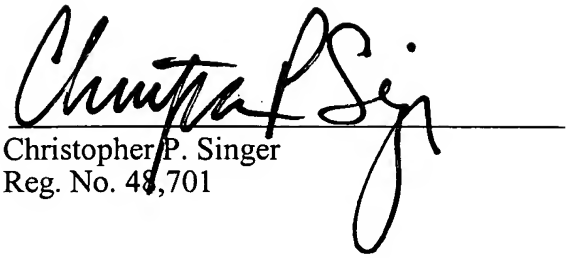
By: 
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